MOLECULAR BASIS AND MODIFICATION OF A NEURAL CREST DEFICIT IN A DOWN SYNDROME MOUSE MODEL

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Trisomy 21 occurs in ~1/700 live births and leads to phenotypes associated with Down syndrome (DS), including craniofacial dysmorphism and a small mandible. Ts65Dn mice are trisomic for approximately half the genes on human chromosome 21 and display DS-like craniofacial anomalies. We traced the origin of the small mandible in Ts65Dn mice to a reduced 1st branchial arch (BA1) and deficits in neural crest (NC) migration from the neural tube (NT) and BA1 proliferation around embryonic day 9.5 (E9.5). At E13.5, the small trisomic mandibular precursor persists in Ts65Dn embryos. DYRK1A and RCAN1 are thought to be involved in DS craniofacial development and we hypothesize that dysregulation of Dyrk1a and Rcan1 contributes to the altered craniofacial development in Ts65Dn mice. To test our hypothesis, we quantified expression of Dyrk1a and Rcan1 during embryogenesis. At E9.5, Dykr1a is upregulated and Rcan1 downregulated in Ts65Dn as compared to euploid BA1, yet in the Ts65Dn E13.5 mandibular precursor, Rcan1 is upregulated and Dyrk1a is downregulated. Cells cultured from Ts65Dn and normal BA1 and NT were used to analyze the effects of genetic dysregulation on cell proliferation and migration. In vitro studies revealed the proliferation deficit in trisomic BA1, but not NT, could be attenuated with the green tea polyphenol epigallocatechin gallate (EGCG, known to modulate the effects of Dyrk1a). Additionally we are assessing the effect of EGCG on migration deficits in trisomic NC. Our results provide information about the molecular basis of DS craniofacial abnormalities and may lead to evidenced-based therapeutic options.